Traumatology and Orthopaedics of Kazakhstan
ISSN - e2789-9640

Review

Giant Cell Tumor of Bone in the Era of Denosumab: Indications, Outcomes and Controversies

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Received: April 19, 2026
Revised: May 17, 2026
Accepted: June 02, 2026
Published: June 30, 2026

Citation: Ferid Abdullaliyev. Giant Cell Tumor of Bone in the Era of Denosumab: Indications, Outcomes and Controversies. Trauma & Ortho Kaz, 2026, 77 (3), jto056. https://doi.org/10.52889/1684-9280-2026-77-3-jto056

Abstract

Giant cell tumor of bone is a locally aggressive neoplasm characterized by RANKL-driven osteoclast activation. Denosumab has significantly changed its management.

The objective of the review was to analyze the results and controversies of the use of denosumab in giant cell tumor of bone, clinical outcomes and unresolved controversies to make clinical decisions and identify priority areas for future research.

Methods. A narrative review was performed using PubMed, EMBASE, and Cochrane databases (2010–2025). Studies were selected based on relevance, study design, and clinical impact, including randomized trials, prospective studies, and large retrospective series. The collected data were reviewed and synthesized with particular focus on tumor biology, indications for denosumab therapy, treatment outcomes, recurrence patterns, adverse effects, resistance mechanisms, and current controversies related to the management of giant cell tumor bone.

Results. Denosumab demonstrates high response rates and reduces surgical morbidity for giant cell tumor bone. However, concerns remain regarding recurrence, treatment duration, and long-term safety.

Conclusion. Denosumab is an effective treatment option in selected patients, but careful patient selection and long-term monitoring are essential.

Keywords: giant cell tumor of bone, denosumab, RANKL, osteoclastoma, bone neoplasms, neoadjuvant therapy, malignant transformation, recurrence.

1. Introduction

Giant cell tumor of bone (GCTB) is a primary, locally aggressive, benign bone neoplasm that accounts for approximately 3–8% of all primary bone tumors and up to 20% of benign bone neoplasms on a global scale. The first documented instance of this condition was by Sir Astley Cooper in 1818, and it was subsequently thoroughly delineated by Jaffe, Lichtenstein, and Portis in the mid-20th century. GCTB remains a significant challenge for clinicians due to its erratic biological behaviour, tendency for local recurrence, and, although rare, documented capacity for distant metastasis and malignant transformation [1].

The tumor predominantly affects skeletally mature young adults, with a peak incidence in the third and fourth decades of life and a slight female predominance. GCTB most frequently involves the epiphyseal region of long bones, particularly the distal femur, proximal tibia, and distal radius, although virtually any bone can be affected. Axial skeletal involvement, especially that of the spine and sacrum, has been shown to be associated with a higher degree of surgical complexity and an increased risk of neurological compromise [2,3].

Histologically, GCTB is composed of three cell populations: mononuclear stromal cells (the true neoplastic component), mononuclear monocytic precursor cells, and multinucleated osteoclast-like giant cells. The molecular pathogenesis of GCTB was substantially elucidated following the discovery that neoplastic stromal cells harbor mutations in the H3F3A gene encoding histone H3.3 in over 90% of cases, most

commonly the p.Gly34Trp (G34W) substitution. Stromal cells exhibit aberrant overexpression of receptor activator of nuclear factor kappa-B ligand (RANKL). This expression drives the recruitment, differentiation, and activation of osteoclast-like giant cells. These cells drive the characteristic bone destruction [4-6].

This mechanism provides the rationale for targeting the RANK/RANKL/OPG axis. Denosumab is a fully human IgG2 monoclonal antibody targeting RANKL and was approved by the U.S. Food and Drug Administration (FDA) in 2013 and the European Medicines Agency (EMA) in 2014 specifically for the treatment of adults and skeletally mature adolescents with GCTB that is unresectable or where surgical resection would result in severe morbidity. This approval was based on the findings of two phase II prospective trials, which represented the first targeted pharmacological therapy to be approved for this disease [7].

Clinical experience with denosumab has increased over the past decadein, the clinical experience with denosumab in GCTB. Its use has been extended beyond the initially approved indication to encompass neoadjuvant treatment prior to surgery, management of pulmonary metastases, spinal cord compression, paediatric cases, and as an adjunct to intralesional curettage. Nevertheless, this expanding application has been accompanied by growing recognition of significant controversies. These include concerns about the optimal duration of therapy, high recurrence rates following drug discontinuation, the risk of malignant transformation, and the long-term consequences of prolonged RANKL inhibition on the skeleton [8,9].

This review provides an evidence-based overview of the indications, outcomes, and controversies of denosumab in GCTB, clinical outcomes, and unresolved controversies surrounding the utilisation of denosumab in the management of GCTB, with the aim of guiding clinical decision-making and identifying priority areas for future research.

To our knowledge, this is one of the most comprehensive reviews integrating surgical and systemic perspectives in the management of GCTB.

2. Materials and Methods

A narrative literature review was conducted to evaluate the current evidence regarding the role of denosumab in the management of giant cell tumor of bone (GCTB). A comprehensive literature search was performed using the PubMed, Scopus, and Google Scholar databases for studies published between January 2010 and March 2025. The search strategy included combinations of the following keywords: “giant cell tumor of bone”, “GCTB”, “denosumab”, “RANKL”, “osteoclast”, “recurrence”, “neoadjuvant therapy”, “malignant transformation”, and “bone tumor”. Only articles published in English were included. Randomized clinical trials, prospective and retrospective cohort studies, systematic reviews, meta-analyses, review articles, and clinically significant case reports were evaluated according to their scientific relevance and contribution to current clinical practice. Additional relevant studies were identified through manual screening of the reference lists of selected articles. The collected data were reviewed and synthesized with particular focus on tumor biology, indications for denosumab therapy, treatment outcomes, recurrence patterns, adverse effects, resistance mechanisms, and current controversies related to the management of GCTB.

3. Pathobiology of GCTB: the RANKL axis as a therapeutic target

Cellular Composition and the Neoplastic Stromal Cell

The cellular architecture of GCTB has been the subject of extensive investigation. The contemporary consensus identifies the mononuclear spindle-shaped stromal cell as the true neoplastic element of the tumor, a view supported by evidence that these cells harbour the H3F3A driver mutations, exhibit clonal expansion, and demonstrate anchorage-independent growth in vitro. In contrast, the osteoclast-like giant cells and mononuclear monocytic precursors are regarded as reactive, non-neoplastic components. These components are recruited and activated by signals emanating from the stromal cells [9].

The H3F3A G34W mutation, identified by Behjati et al. in 2013, has been shown to be highly specific for GCTB and is now widely recognised as a valuable diagnostic marker, particularly in challenging histological scenarios. The H3F3A mutation alters chromatin remodeling, causes epigenetic dysregulation, and increases RANKL expression. These changes promote osteoclastogenesis and bone destruction [10].

The RANK/RANKL/OPG Pathway

RANKL, a member of the tumor necrosis factor (TNF) superfamily, is the principal mediator of osteoclast differentiation and function. In the process of physiological bone remodelling, RANKL, which is produced by osteoblasts and stromal cells, binds to its cognate receptor RANK on osteoclast precursors, thereby promoting their differentiation into mature,

https://doi.org/10.52889/1684-9280-2026-77-3-jto056

bone-resorbing osteoclasts. Osteoprotegerin (OPG), a decoy receptor for RANKL, competitively inhibits this interaction, thereby functioning as a natural brake on osteoclastogenesis [11,12].

In GCTB, neoplastic stromal cells produce RANKL in supraphysiological quantities, thereby overwhelming the endogenous OPG-mediated regulatory mechanism. The resultant unchecked osteoclast activation leads to progressive, expansile bone destruction, which is the pathological hallmark of the disease. It is imperative to note that this RANKL overexpression is not merely a secondary phenomenon; rather, it is directly linked to the underlying H3F3A mutation and resultant epigenetic alterations [10,13].

Denosumab, by binding RANKL with picomolar affinity and preventing its interaction with RANK, effectively neutralises this pathological drive, leading to apoptosis of osteoclast-like giant cells and cessation of bone resorption. Histologically, this is reflected in the disappearance of giant cells, fibrous replacement of tumor stroma, new bone formation at the tumor periphery, and development of a fibro-osseous shell. Collectively, these phenomena represent the morphological correlate of clinical response [14,15].

Molecular Subtypes and Biological Behavior

Recent genomic studies have identified molecular heterogeneity within GCTB that extends beyond the H3F3A G34W mutation. A minority of cases exhibit H3F3A G34L or G34V substitutions, while rare tumors demonstrate wild-type H3F3A. The biological significance of these variants remains to be elucidated. Furthermore, secondary genetic events, including copy number alterations, mutations in cell cycle regulators, and activation of oncogenic signalling pathways, have been implicated in the rare progression from conventional GCTB to secondary malignant GCTB. This transformation has been reported in approximately 1–3% of cases, with a marked increase observed in patients who have received prior radiotherapy [5].

4. Clinical presentation, diagnosis, and staging

Clinical Features

GCTB is characterised by the presence of localised pain, swelling, and restricted joint motion at the affected site. The onset of the condition is frequently insidious, with symptoms manifesting over a period of weeks to months before a definitive diagnosis can be made. The occurrence of pathological fracture at the time of presentation has been documented in 10–35% of cases, a proportion that is especially high in tumors involving the distal radius or the proximal humerus. This factor has been shown to have a significant impact on both surgical planning and oncological outcomes. The involvement of the spine and sacrum may present with radiculopathy, myelopathy, or bowel or bladder dysfunction when neurological structures are compromised [16,17].

Imaging Characteristics

Plain radiography typically demonstrates an eccentric, lytic, epiphyseal lesion with well-defined non-sclerotic margins ('geographic' pattern) and cortical expansion or thinning without periosteal reaction or mineralized matrix. The absence of internal matrix mineralization is a distinguishing feature of GCTB, setting it apart from other matrix-producing lesions, including chondroblastoma [18].

Magnetic resonance imaging (MRI) is considered the gold standard for local staging, providing superior delineation of marrow involvement, soft tissue extension, joint infiltration, and proximity to neurovascular structures. CT scanning is an invaluable tool in this regard, offering superior assessment of cortical integrity and extraosseous extension, in addition to facilitating preoperative planning. Whole-body bone scintigraphy and FDG-PET/CT may be employed for the detection of metastatic disease, particularly pulmonary metastases, which occur in 1–4% of cases [18].

Histopathological Diagnosis and H3F3A Immunohistochemistry

Core needle biopsy under radiological guidance is the preferred diagnostic approach for accessible lesions. Histological examination reveals a characteristic triad of mononuclear stromal cells, mononuclear monocytic cells, and uniformly distributed multinucleated osteoclast-like giant cells. Histological grade does not consistently predict clinical behaviour. The Campanacci radiological grading system (Grades I–III based on extent of cortical involvement and extraosseous extension) is therefore a more reliable predictor of clinical outcomes and is recommended for surgical planning [19,20].

The anti-H3.3 G34W mutant-specific antibody (clone RM193, Sigma-Aldrich) has demonstrated sensitivity and specificity exceeding 95% for GCTB in a substantial validation series. This provides a valuable ancillary immunohistochemical marker, particularly in difficult cases, small biopsies, or denosumab-treated specimens where the characteristic histological features may be significantly altered [9,10].

Staging Systems

There is an absence of a universally accepted and validated staging system that is specific to GCTB. The ENKAMING surgical staging system is a three-stage classification system for benign bone tumors (latent,

https://doi.org/10.52889/1684-9280-2026-77-3-jto056

active, aggressive). However, this system has limited prognostic precision for GCTB. The Campanacci radiological grading system is more extensively utilised in clinical practice. Recently, the GCTB Study Group advanced a comprehensive staging framework that incorporates imaging, histology, molecular data and metastatic status. Nonetheless, prospective validation of this framework remains in progress [21].

5. Surgical management: the evolving standard

Intralesional Curettage and Local Adjuvants

Intralesional curettage, with or without local adjuvant therapy (phenol, hydrogen peroxide, argon beam coagulation, or cryotherapy), followed by bone grafting or polymethylmethacrylate (PMMA) cement filling, remains the primary treatment for the majority of accessible GCTB (Campanacci Grades I and II) in anatomically suitable locations. The merits of joint-preserving surgery are manifold. Its benefits include functional preservation, reduced surgical morbidity and the avoidance of prosthetic complications in a predominantly young patient population [22,23].

Local recurrence following intralesional curettage ranges from 12% to 40% in large case series, influenced by Campanacci grade, adequacy of curettage margins, use of local adjuvants, and anatomical location. It is generally accepted that recurrences are amenable to repeat curettage, with cumulative recurrence rates plateauing after the second surgical intervention [24].

En Bloc Resection

Wide en bloc resection with appropriate margins is indicated for Campanacci Grade III tumors with extensive extraosseous soft tissue involvement, expendable bone locations (fibular head, proximal ulna, coccyx), pathological fractures where joint salvage is not feasible, and recurrent disease after multiple curettages. Although resection offers the lowest local recurrence rate (approximately 5–7%), it is associated with significant functional morbidity and requires complex reconstruction strategies, including structural allografts, prosthetic arthroplasty, or combined biological/prosthetic solutions [2,17].

Special Anatomical Considerations

The presence of spinal and sacral GCTB gives rise to a unique set of surgical challenges. These are a result of the proximity of the tumors to neural elements, the complex nature of the vascular anatomy, and the difficulty in achieving wide margins. A total en bloc spondylectomy (TES) may be technically feasible for selected sacral and mobile spine cases, and offers the best local control rates. However, it is associated with significant morbidity, including neurological deficit, wound complications, and postoperative instability. Preoperative embolisation is a frequently employed technique in order to reduce intraoperative haemorrhage in cases of vascular sacral lesions [25,26].

6. Denosumab in GCTB: Mechanism, pharmacology, and pivotal trials

Mechanism of Action and Pharmacology

Denosumab is a fully human IgG2 monoclonal antibody that binds to RANKL with extremely high affinity (KD approximately 3×10−12 M), thereby preventing its interaction with RANK on osteoclast precursors and consequently blocking osteoclast formation, function, and survival. The pharmacokinetic profile is characterised by subcutaneous administration, a prolonged half-life of approximately 25–28 days, and non-linear, target-mediated disposition kinetics. The approved dosing regimen consists of for GCTB, which has been shown to result in maximal RANKL suppression (as measured by serum CTX-I) when administered as a subcutaneous injection at a dose of 120 mg every four weeks, with loading doses on days 8 and 15 of cycle 1. The results demonstrate that this dosing regimen achieves maximal RANKL suppression rapidly and sustains it throughout treatment [27,28].

Landmark Clinical Trials

The pivotal evidence supporting denosumab approval in GCTB derives from an open-label, phase II trial (study 20062004) conducted by Amgen and published by Chawla et al. (2013). The present trial comprised three cohorts of patients: Cohort 1 (n=37) comprised patients with unresectable GCTB. Cohort 2 (n=101) comprised patients with resectable GCTB for whom planned surgery was associated with severe morbidity (limb amputation, joint resection or hemipelvectomy). Cohort 3 (n=218) included patients with GCTB in a compassionate-use or post-approval setting [7].

The primary endpoint was defined as the response of the tumor, which was measured in two ways: (1) the presence of ≥90% giant cell elimination on histological assessment, or (2) the absence of radiological progression of the target lesion. In the combined analysis of Cohorts 1 and 2, the objective response rate was found to be 86%, with 96% of evaluable patients demonstrating no radiological disease progression at 25 weeks. It is noteworthy that 74% of patients in Cohort 2 who were scheduled for resection underwent a less-morbid surgical procedure following denosumab treatment. The results of the study demonstrated the efficacy of denosumab as the first systemic agent for GCTB, thus leading to its regulatory approval [7].

https://doi.org/10.52889/1684-9280-2026-77-3-jto056

Long-Term Follow-Up Data

A substantial body of evidence from study 20062004, as reported by Rutkowski et al. (2015), in conjunction with subsequent analyses, has demonstrated that the clinical benefit was sustained with ongoing therapy in the majority of patients. However, these data also revealed that disease progression occurred in a subset of patients despite ongoing denosumab treatment, and that recurrence was common following treatment discontinuation. Following a 24-month period of observation, the overall survival rate was found to be in excess of 95% in both cohorts. This finding is indicative of the predominantly benign nature of GCTB. However, it is also important to note that response endpoints, rather than survival rates, are the meaningful clinical metrics in this disease [29].

Subsequent Prospective Studies and Registries

Subsequent studies, both prospective and retrospective, have validated the efficacy findings of the pivotal trial. The GiST-study (Giant Cell Tumor Study), a multicenter German registry, enrolled over 200 patients and confirmed response rates of 83–91% with denosumab, while highlighting variability in local recurrence rates (15–50%) following treatment discontinuation and surgery. The Italian Sarcoma Group registry similarly reported a radiological response in 89% of evaluable patients, with downstaging of planned surgery in 68% of initially resectable cases [30].

7. Current indications for denosumab in GCTB

FDA/EMA-Approved Indication: Unresectable GCTB

The regulatory-approved indication for denosumab encompasses adults and skeletally mature adolescents with GCTB that is unresectable, or resectable only through surgical procedures associated with severe morbidity, such as joint resection, limb amputation, or hemipelvectomy. This indication is based on the demonstration of durable disease control and downstaging of surgical requirements in the pivotal trial. Clinical scenarios that meet this threshold include locally advanced sacral, spinal, and pelvic GCTB; tumors involving critical anatomical structures, such as major vessels, the spinal cord, or the brachial plexus; and recurrent disease in previously operated patients where further surgery would result in a major functional deficit [8,31].

Neoadjuvant Denosumab Prior to Surgery

The neoadjuvant application of denosumab, whereby the drug is administered prior to planned surgery with the objective of reducing tumor volume, inducing cortical reconstitution and reducing the extent of necessary surgical intervention, has emerged as one of the most clinically significant applications of the agent. Evidence from the phase II trial indicates that the administration of neoadjuvant denosumab resulted in surgery that was less extensive in 74% of patients in Cohort 2. This finding has the potential to obviate the necessity for joint resection or amputation [7].

The optimal duration of neoadjuvant therapy prior to surgery remains undefined. The majority of published series have employed 3–6 months (3–6 cycles) of preoperative denosumab, with some authors advocating for longer courses (9–12 months) in complex cases where greater tumor consolidation and cortical reconstitution are desired. Prolonged neoadjuvant denosumab therapy can induce dense fibro-osseous transformation of the tumor. This transformation has been shown to significantly increase the technical difficulty of surgery, as the transformed tissue is markedly harder to curet and may obscure tumor-normal bone interfaces [17].

A critical yet underappreciated concern regarding neoadjuvant denosumab pertains to its impact on histological diagnosis. Denosumab treatment has been shown to cause the complete elimination of osteoclast-like giant cells and extensive fibrosis, which renders the surgical specimen virtually uninterpretable by conventional histological criteria. The H3F3A G34W immunohistochemical stain retains its diagnostic utility in this particular context. It is therefore recommended that this stain be routinely applied to post-denosumab specimens [32,33].

Adjuvant Denosumab Following Intralesional Curettage

The role of adjuvant postoperative denosumab following intralesional curettage is a subject of considerable debate within the field of GCTB management. The theoretical underpinning of this approach is compelling, as the elimination of residual viable GCTB cells at the curettage margin has the potential to reduce local recurrence rates. Nevertheless, there is an absence of robust prospective randomised evidence that would provide support for this practice. Furthermore, the retrospective data are conflicting [8,34,35].

A multicentre retrospective analysis by Errani et al. (2018) reported no significant reduction in local recurrence with adjuvant denosumab after curettage compared to surgery alone. Conversely, other series have suggested marginal benefit in high-risk scenarios (Campanacci Grade III, suboptimal margins, or initial pathological fracture). A balanced evaluation of the risks and benefits is imperative when considering the use of adjuvant denosumab, taking into account the

potential for local recurrence and the associated adverse effects, including osteonecrosis of the jaw, hypocalcaemia, and the theoretical possibility of malignant transformation [34].

Pulmonary Metastases from GCTB

Pulmonary metastases occur in 1–4% of GCTB patients and, contrary to conventional oncological paradigms, may exhibit characteristics of indolent behaviour and spontaneous regression. Surgical resection of isolated, resectable pulmonary lesions remains the standard of care and has the potential to be curative. For patients with unresectable, multiple, or progressive pulmonary metastases, denosumab represents a pharmacological option that has proven effective, with documented radiological responses and prolonged disease stability in published series [17].

The landmark phase II trial included a small number of patients with pulmonary metastases, demonstrating objective responses in this subset. Subsequent case series and retrospective analyses have further supported the efficacy of denosumab in this setting. Nevertheless, the issue of whether to administer treatment to all patients with GCTB pulmonary metastases or to adopt a watchful waiting approach for asymptomatic, indolent lesions remains unresolved [7,36].

Spinal and Sacral GCTB

GCTB of the spine and sacrum constitutes approximately 5–10% of all GCTB cases and is associated with disproportionately high morbidity. Whilst total en bloc spondylectomy is associated with the best local control, there are significant risks of neurological deficit, massive haemorrhage, wound complications, and mechanical instability. Denosumab is an effective treatment option in this setting. It is used as primary therapy in inoperable cases and as neoadjuvant treatment to facilitate surgical planning and reduce intraoperative haemorrhage [25,37].

The hypothesis under investigation is that preoperative embolization combined with denosumab is a synergistic approach for hypervascular sacral GCTB. The induction of cortical reconstitution and tumor consolidation by denosumab may facilitate safer surgical access and improve the feasibility of en bloc resection. Nevertheless, the issues concerning heightened tissue density and modified tumor-bone interfaces following extended denosumab therapy are equally pertinent in this scenario [38,39].

Denosumab in Pediatric and Adolescent Patients

The utilisation of denosumab in skeletally immature patients (open physes) necessitates particular caution, as RANKL plays a critical physiological role in bone modelling during growth. Case reports and small case series have documented the occurrence of dense metaphyseal banding, physeal bridging, and growth disturbance in paediatric patients receiving denosumab, phenomena analogous to those observed with bisphosphonates. The regulatory approval explicitly restricts the use of the product to skeletally mature adolescents and adults. In cases where the administration of denosumab is deemed essential in younger patients, it is imperative to meticulously evaluate the risk-benefit ratio on an individualised basis. Moreover, stringent monitoring of growth parameters is mandatory to ensure optimal outcomes [40,41].

8. Clinical outcomes: Efficacy, recurrence, and functional results

Radiological and Histological Response

Denosumab has been shown to induce a distinctive and reproducible pattern of radiological response in GCTB. Following the initiation of therapy, sequential imaging techniques have been shown to typically demonstrate progressive peripheral new bone formation and cortical reconstitution. Additionally, the development of a calcified rim at the tumor margin, increased lesion density on CT scans, and a decrease in lesion vascularity on dynamic contrast-enhanced MRI scans have been observed. True tumor shrinkage, i.e. volumetric reduction, is subject to variation and may lag behind the histological and clinical response [42,43].

Histologically, denosumab has been shown to induce the elimination of osteoclast-like giant cells (the RANKL-dependent component), leaving mononuclear stromal cells embedded in a fibro-osseous matrix rich in woven bone. This transformation of the histological appearance, whilst reflecting drug response, should not be confused with resolution of the neoplastic process. This is due to the persistence of residual viable stromal cells, which are the source of recurrence following drug withdrawal [13,15].

Local Recurrence: The Achilles Heel of Denosumab Therapy

Local recurrence following denosumab treatment and surgery represents the most significant clinical challenge in denosumab-treated GCTB. The recurrence rate following denosumab therapy and subsequent curettage has been reported to range from 15% to 50% across various published series. This figure stands in stark contrast to the 12–35% recurrence rate reported in untreated tumors following curettage alone. The recurrence rate following en bloc resection subsequent to denosumab therapy is considerably lower (5–10%), yet it is associated with greater initial surgical morbidity [2,35].

https://doi.org/10.52889/1684-9280-2026-77-3-jto056

A number of hypotheses have been advanced to explain the apparently paradoxical increase in recurrence rates following denosumab-facilitated surgery. Firstly, the dense fibro-osseous transformation induced by denosumab has the potential to obscure residual tumor, thereby rendering complete curettage more challenging. Secondly, denosumab may exert a more effective effect as a cytostatic rather than a cytotoxic agent on neoplastic stromal cells, thus leaving a viable neoplastic population that reactivates upon drug withdrawal. Thirdly, the presence of selection bias in studies that offer less-morbid surgery subsequent to denosumab (i.e. the acceptance of higher curettage rates for originally grade III tumors) has the potential to artificially inflate recurrence rates in comparison with historical controls [32,44].

A systematic review and meta-analysis has demonstrated higher local recurrence rates in patients treated with preoperative denosumab followed by curettage compared to curettage alone, highlighting the need for careful patient selection and surgical planning [35].

Functional Outcomes and Quality of Life

The primary objective of denosumab-facilitated surgical downgrading is the preservation of function. A substantial body of research has documented superior functional outcomes in patients who underwent joint-preserving surgery facilitated by denosumab in comparison to historical cohorts requiring resection arthroplasty. The Musculoskeletal Tumor Society (MSTS) scores and the Toronto Extremity Salvage Scores (TESS) have been shown to be consistently higher in patients who preserve native joint anatomy [29,30].

A quality-of-life analysis, which was embedded within the German GiST registry, documented significant improvements in patient-reported outcome measures (PROMs). These improvements were reflected in pain visual analogue scores, EORTC QLQ-C30, and disease-specific functional scales. These improvements were observed following denosumab initiation, even prior to surgery. This is indicative of the symptomatic benefit of halting bone destruction [31].

9. Controversies in Denosumab use for GCTB

Optimal Duration of Therapy

The optimal duration of denosumab therapy prior to surgery, and the question of whether to continue treatment postoperatively, remain some of the most contentious issues in the field. There is an absence of prospective randomised evidence to guide this decision. The current practice of preoperative therapy varies considerably across institutions, with durations ranging from 2 to 24+ months. It is hypothesised that shorter preoperative courses (3–4 months) may not achieve maximal cortical reconstitution and tumor consolidation. Conversely, longer courses (>6 months) may increase fibro-osseous transformation to a degree that complicates surgery and paradoxically increases recurrence risk [45,46].

In the case of patients treated with denosumab as primary definitive therapy (unresectable disease), no defined endpoint of therapy has been established, and many patients remain on indefinite treatment. The safety and long-term consequences of treatment extending beyond two to three years are poorly characterised. Furthermore, the optimal surveillance strategy for patients on chronic denosumab therapy has not been prospectively validated [15,31].

Recurrence Following Denosumab Discontinuation

The reappearance of tumors following the cessation of denosumab treatment is a significant concern, particularly in patients who have undergone definitive treatment without surgical intervention. A substantial body of research has documented radiological and clinical recurrence within a period of 6–18 months of drug discontinuation in 15–50% of patients. The highest recurrence rates have been observed in patients treated for unresectable disease who never underwent surgery [31,47].

The biological basis of this phenomenon is the persistence of viable neoplastic stromal cells throughout denosumab treatment, which, upon restoration of RANKL signalling, re-recruit osteoclast precursors and re-initiate the destructive cycle. It is imperative to acknowledge the significant practical ramifications of this observation. In the majority of clinical scenarios, the treatment of denosumab should not be regarded as a curative intervention when administered as a standalone modality. It is, therefore, essential that treatment discontinuation planning incorporates a surgical or radiotherapeutic strategy for the consolidation of the disease [13,44].

Malignant Transformation Risk

Malignant transformation in GCTB, defined as the development of a high-grade sarcoma within a conventional GCTB, is a well-recognised, albeit rare, complication estimated to occur in 1–3% of cases in the general GCTB population. It is evident from a historical perspective that there was a strong association between this risk and prior external beam radiotherapy. This association was the primary reason for the abandonment of radiotherapy as a standard treatment modality for GCTB [44,48].

https://doi.org/10.52889/1684-9280-2026-77-3-jto056

The controversy surrounding the potential of denosumab to augment the risk of malignant transformation in GCTB remains unresolved. Case reports and small case series have documented secondary osteosarcoma, undifferentiated pleomorphic sarcoma, and other high-grade sarcomas arising during or after denosumab therapy. Recent reviews have emphasised that many reported cases involved prolonged denosumab exposure, prior radiotherapy, or multiple previous surgeries, making a definitive causal association difficult to establish [49,50].

The mechanistic basis of possible denosumab-associated malignant transformation remains speculative. Proposed explanations include alterations in stromal cell biology, effects on the tumor microenvironment, and selection of clones harboring additional oncogenic events. Although this potential risk is recognized, it does not preclude denosumab use; rather, it highlights the importance of close surveillance and repeat biopsy of any lesion showing unexpected progression during treatment [49,50].

Defining Radiological Response: Limitations of Conventional Criteria

The evaluation of treatment response in patients with GCTB who have been administered denosumab cannot be reliably performed using conventional oncological response criteria, such as RECIST (Response Evaluation Criteria in Solid Tumors), which rely on the measurement of lesion size. Denosumab has been observed to induce peripheral new bone formation, which may initially manifest as an increase in lesion density or size on imaging. This phenomenon can result in a misclassification of responding tumors as progressive disease according to size-based criteria [42,51].

Emerging response assessment approaches for GCTB include volumetric MRI-based response criteria (incorporating T2 signal changes and enhancement patterns), FDG-PET-based metabolic response criteria (with SUV reduction reflecting reduced osteoclastic activity), and combined histological-radiological composite endpoints. It is imperative that standardisation of response assessment is implemented across clinical trials, with a view to facilitating valid cross-study comparisons [15,52].

Denosumab in the Setting of Intralesional Curettage: Does It Help or Harm?

The role of perioperative denosumab in patients with resectable GCTB remains controversial. While some studies suggest that neoadjuvant therapy may reduce tumor vascularity and facilitate less morbid surgery, others have reported increased surgical difficulty due to fibro-osseous transformation and potentially higher recurrence rates following curettage. Robust prospective evidence to resolve this issue is lacking [16,34].

This controversy underscores the imperative for prospective randomised controlled trials directly comparing curettage with and without denosumab in resectable GCTB. The GDCT (Giant Cell Denosumab Clinical Trial) and associated investigator-initiated protocols are seeking to address this issue. However, the enrolment and long-term follow-up of participants have proven challenging in this relatively rare disease [45,53].

Long-Term Skeletal Safety and Adverse Effects

Prolonged RANKL inhibition with denosumab has well-characterised skeletal consequences derived from its extensive use in osteoporosis and bone metastasis settings. Osteonecrosis of the jaw occurs in 1–5% of patients receiving high-dose denosumab, with an increased risk associated with treatment duration, dental procedures, and poor oral hygiene. Atypical femoral fractures may occur with prolonged use, particularly beyond 3–5 years. Rebound hypercalcemia may occur after denosumab discontinuation, attributable to the sudden resurgence of RANKL signalling and consequent rapid bone resorption. This phenomenon is of particular clinical significance in GCTB patients in whom treatment discontinuation is being planned [54,55].

The rebound hypercalcemia phenomenon following denosumab discontinuation in GCTB merits particular emphasis. Cases of severe, symptomatic hypercalcemia requiring hospitalisation and intravenous bisphosphonate therapy have been reported in the weeks following denosumab cessation. The risk may be reduced with bridging therapy, with zoledronic acid or alendronate following the discontinuation of denosumab. However, evidence remains limited to support the existence of standardised protocols for this transition, and that such protocols have not been prospectively validated [55,56].

Role of Radiotherapy in the Denosumab Era

Radiotherapy may be considered in denosumab-refractory cases for unresectable GCTB, due to its documented efficacy (local control rates of 70–80%) but also significant concerns regarding radiation-associated malignant transformation. The advent of denosumab has led to a substantial reduction in the utilisation of radiotherapy as the primary local treatment modality in the majority of cases of unresectable GCTB.

https://doi.org/10.52889/1684-9280-2026-77-3-jto056

Nonetheless, for patients with genuine denosumab-refractory disease or those for whom surgical consolidation is not viable despite adequate RANKL inhibition, radiotherapy – particularly stereotactic body radiotherapy (SBRT) with its superior dose conformality – may still have a role as consolidative or salvage treatment [57,58].

10. Special populations and scenarios

Pregnancy and GCTB

GCTB may be diagnosed during pregnancy, which can present management dilemmas due to the teratogenic potential of denosumab and the need to balance maternal and fetal well-being. Denosumab has been demonstrated to cross the placenta in experimental models, resulting in developmental abnormalities, particularly those affecting the skeleton and the formation of lymph nodes. Women of reproductive age should use effective contraception during denosumab therapy and the drug is contraindicated in pregnancy. In the case of pregnant patients diagnosed with GCTB, management should be individualized with multidisciplinary follow-up. The plan may include a delay in systemic treatment until the postpartum period, or cautious consideration of surgical intervention during the second trimester [53,59].

Denosumab-Refractory GCTB

A minority of GCTB patients demonstrate primary or acquired resistance to denosumab, manifesting as progressive disease on imaging despite adequate drug exposure. The mechanisms of denosumab resistance are not fully understood, but may include RANK-independent osteoclastogenesis (via M-CSF, EGF, or other signalling pathways), upregulation of alternative RANKL production by non-stromal tumor components, or emergence of stromal cell subclones with intrinsic resistance mechanisms. The management of denosumab-refractory GCTB is poorly defined. Treatment options include surgery, bisphosphonates, radiotherapy, and clinical trials targeting alternative signalling pathways [60].

Giant Cell Tumor of Tendon Sheath (TGCT/PVNS)

GCTB should be distinguished from tenosynovial giant cell tumor (TGCT), formerly termed pigmented villonodular synovitis (PVNS), which involves synovial tissue and has a distinct molecular driver (CSF1 overexpression due to chromosomal translocation). Pexidartinib, a CSF1R inhibitor, has FDA approval for the treatment of symptomatic TGCT, while denosumab is not indicated and has been demonstrated to be ineffective for this disease entity. The incorrect classification of these entities has the potential to result in the selection of an inappropriate treatment [61,62].

11. Emerging therapies and future directions

Novel RANKL Pathway Inhibitors

Research into next-generation RANKL pathway inhibitors is ongoing. The introduction of biosimilar denosumab products into the market has the potential to enhance global access to RANKL-targeted therapy. Furthermore, novel formulations and delivery strategies are currently under preclinical investigation. These include extended-release subcutaneous formulations and OPG-Fc fusion proteins. However, to date, none have demonstrated clinical utility in GCTB [53,63].

Combination Strategies

The combination of denosumab with anti-angiogenic agents (e.g. pazopanib, sorafenib), mTOR inhibitors, or immunotherapy has been proposed as a strategy to target both the osteoclastic component (via RANKL inhibition) and the neoplastic stromal cell population. The rationale for combining denosumab with agents targeting the PDGFR and EGFR pathways overexpressed in GCTB stromal cells is supported by preclinical data. Early-phase clinical trials are underway [13,53].

H3F3A-Targeted Approaches

The near-universal presence of H3F3A driver mutations in GCTB stromal cells represents an attractive therapeutic target. This review investigates the potential of epigenetic therapies that target the downstream consequences of histone H3.3 G34W mutation. This includes the use of HDAC (Histone Deacetylase) inhibitors and BET (Bromodomain) inhibitors, which are currently under preclinical evaluation. The high specificity of H3.3 G34W for GCTB renders it an attractive target for cell-based immunotherapy approaches, including TCR-engineered T-cell therapies. However, it should be noted that clinical translation remains at an early stage [5].

Biomarker Development

The identification of reliable predictive biomarkers for denosumab response, recurrence risk, and malignant transformation risk is a significant unmet need.

https://doi.org/10.52889/1684-9280-2026-77-3-jto056

The present investigations include the detection of H3F3A mutations in plasma (liquid biopsy), serum bone turnover markers (CTX-I, P1NP, TRACP-5b), and imaging-based radiomic signatures derived from MRI and FDG-PET. The validation of candidate biomarkers within ongoing registries is a research priority [5].

12. Proposed clinical management algorithm

In consideration of the extant evidence, the following stepwise management framework is proposed for GCTB in the denosumab era. It is recognised that all treatment decisions should be made within a multidisciplinary team (MDT) comprising orthopedic oncology, medical oncology, radiology, pathology, and radiation oncology:

Step 1 — Comprehensive staging: All patients should undergo plain radiography, MRI (local), CT chest (pulmonary metastases), and biopsy with H3F3A G34W immunohistochemistry. Campanacci radiological grading should be assigned.

Step 2 — Surgical feasibility assessment: Determination of whether the tumor is (a) resectable with acceptable morbidity, (b) resectable only with severe morbidity, or (c) unresectable.

Step 3a — Resectable GCTB with acceptable morbidity (Campanacci I–II): Proceed to intralesional curettage with local adjuvant and PMMA/bone graft. Denosumab is not routinely indicated but may be considered in selected high-risk cases within a clinical trial setting.

Step 3b — Resectable GCTB with severe morbidity: Consider neoadjuvant denosumab for 3–6 months followed by MDT reassessment for surgical downstaging. If downstaging is achieved, proceed to less-morbid surgery. If not, reassess for en bloc resection or continued Denosumab.

Step 3c — Unresectable GCTB: Initiate denosumab as primary treatment. Reassess every 3–6 months for conversion to surgical eligibility. If feasible, surgical consolidation is preferred over indefinite medical therapy.

Step 4 — Surveillance: All patients require long-term follow-up (minimum 5 years, ideally 10 years) with periodic imaging. Post-denosumab patients require heightened surveillance for recurrence, particularly in the 12–24 months following treatment discontinuation.

13. Discussion

Denosumab has undoubtedly transformed the management of GCTB, providing the first effective systemic therapy for a disease previously managed almost exclusively by surgery. Its ability to induce tumor response, consolidate cortical integrity, downgrade surgical requirements, and control unresectable or metastatic disease has resulted in significant clinical benefits for patients, including functional preservation and improved quality of life.

Nevertheless, denosumab is not a cure. The elevated incidence of local recurrence following the cessation of drug administration and surgical intervention, the potential for malignant transformation – albeit infrequent – the intricacy of histological evaluation in treated specimens, and the prolonged skeletal safety concerns collectively emphasise the necessity for judicious utilisation of denosumab, within a framework of rigorous patient selection, clearly defined treatment objectives, and systematic long-term surveillance.

The unresolved controversies surrounding optimal treatment duration, the role of denosumab in the adjuvant setting after curettage, and the management of denosumab-refractory disease represent urgent research priorities. The generation of high-quality evidence is imperative for the refinement of current practices and the establishment of evidence-based guidelines. This evidence can be obtained through the implementation of prospective randomised controlled trials and well-designed multicentre registries. Collaborative international endeavours, such as the GCTB Study Group and the European Musculo-Skeletal Oncology Society (EMSOS) GCTB network, are imperative in propelling this agenda forward.

14. Conclusions

Denosumab can be regarded as a powerful yet nuanced addition to the armamentarium of GCTB treatments. The optimal utilisation of this technology necessitates individualisation, multidisciplinary collaboration, and a comprehensive understanding of its therapeutic potential and limitations.

This review provides a comprehensive and structured synthesis of current evidence, with a particular focus on clinical decision-making and unresolved controversies in denosumab use.

https://doi.org/10.52889/1684-9280-2026-77-3-jto056

Funding. None.
Conflicts of interest. None.

AI Declaration. The author did not use AI or AI-assisted technologies in the preparation of this manuscript.

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Деносумаб дәуіріндегі сүйектің алып жасушалы ісігі: Тағайындауға көрсетілімдер, нәтижелер мен пікірталастар

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https://doi.org/10.52889/1684-9280-2026-77-3-jto056

Түйіндеме

Сүйектің алып жасушалы ісігі — бұл RANKL деңгейімен реттелетін остеокластардың белсендірілуімен сипатталатын, жергілікті агрессивті қатерсіз ісік. Деносумаб оны емдеу тәсілдерін айтарлықтай өзгертті.

Шолу мақсаты сүйектің алып жасушалы ісігінде деносумабты қолданудың нәтижелері мен пікірталастарын талдау, клиникалық шешімдер қабылдау және болашақ зерттеулердің басым бағыттарын анықтау болды.

Әдістері. PubMed, EMBASE және Cochrane мәліметтер базасын пайдалана отырып, талдамалы шолу жүргізілді (2010–2025 жж.). Зерттеулер өзектілігіне, зерттеу дизайнына және клиникалық маңыздылығына қарай іріктелді. Оның ішінде рандомизацияланған сынақтар, проспективті зерттеулер және ауқымды ретроспективті сериялар қамтылды. Жиналған мәліметтер талданып, ісік биологиясына, деносумаб терапиясының көрсетілімдеріне, емдеу нәтижелеріне, ісіктің қайталану сипатына, жағымсыз әсерлеріне, төзімділік механизмдеріне және сүйектің алып жасушалы ісігін емдеуге қатысты қазіргі таңдағы қайшылықтарға ерекше назар аудара отырып жүйеленді.

Нәтижелері. Деносумаб сүйектің алып жасушалы ісігін емдеуде жоғары тиімділік көрсетіп, хирургиялық асқынулар мен мүгедектік деңгейін төмендетеді. Дегенмен, ісіктің қайталануы, емдеу ұзақтығы және ұзақ мерзімді қауіпсіздікке қатысты мәселелер әлі де өзекті болып қалуда.

Қорытынды. Деносумаб — сүйектің алып жасушалы ісігі бар іріктеліп алынған науқастарды емдеудегі тиімді әдіс. Бірақ бұл ретте науқастарды мұқият іріктеу және ұзақ мерзімді бақылау жүргізу өте маңызды.

Түйін сөздер: сүйектің алып жасушалы ісігі, деносумаб, RANKL, остеокластома, сүйек ісіктері, неоадъювантты терапия, қатерлі ісікке айналу, ісіктің қайталануы.

Гигантоклеточная опухоль кости в эпоху Деносумаба: Показания, результаты и дискуссии

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Резюме

Гигантоклеточная опухоль кости представляет собой локально-агрессивное новообразование, характеризующееся RANKL-индуцированной активацией остеокластов. Деносумаб существенно изменил подходы к ведению таких пациентов.

Цель обзора: провести анализ спорных вопросов в результатах применения деносумаба при гигантоклеточной опухоли кости, клинических исходов и нерешенных проблем для принятия клинических решений и определения приоритетных направления для будущих исследований.

Методы. Проведен нарративный обзор литературы с использованием баз данных PubMed, EMBASE и Cochrane (за период 2010–2025 гг.). Отбор публикаций осуществлялся на основе их релевантности, дизайна исследования и клинической значимости; в анализ были включены рандомизированные контролируемые испытания, проспективные исследования и крупные серии ретроспективных наблюдений. Собранные данные были изучены и систематизированы с особым акцентом на биологию опухоли, показания к терапии деносумабом, исходы лечения, характер рецидивирования, побочные эффекты, механизмы резистентности и современные дискуссионные вопросы, связанные с лечением гигантоклеточной опухоли кости.

Результаты. Деносумаб демонстрирует высокую частоту клинического ответа и снижает инвалидизацию после хирургических вмешательств при гигантоклеточной опухоли кости. Тем не менее, вопросы касательно риска рецидивов, оптимальной продолжительности лечения и долгосрочной безопасности остаются нерешенными.

Выводы. Деносумаб является эффективным вариантом лечения гигантоклеточной опухоли кости для определенной группы пациентов, однако критически важными условиями остаются тщательный отбор больных и долгосрочный мониторинг.

Ключевые слова: гигантоклеточная опухоль кости, деносумаб, RANKL, остеокластома, новообразования костей, неоадъювантная терапия, злокачественная трансформация, рецидив.